CLAIMS

1. An attenuated vaccinia virus comprising a mutation in a first gene encoding an interferon-modulating polypeptide that results in the virus lacking at least a first functional interferon-modulating polypeptide, wherein the interferon-modulating polypeptide directly binds interferon.

2. The attenuated vaccinia virus of claim 1, wherein the interferon-modulating polypeptide binds IFN-α or IFN-β.

3. The attenuated vaccinia virus of claim 2, wherein the interferon-binding polypeptide is B18R.

4. The attenuated vaccinia virus of claim 1, wherein the interferon-modulating polypeptide binds IFNγ.

5. The attenuated vaccinia virus of claim 4, wherein the interferon-binding polypeptide is B8R.

6. The attenuated vaccinia virus of claim 1, further comprising a second mutation in at least one of the following:

a) a second gene encoding an interferon-modulating polypeptide that results in the virus lacking at least a second functional interferon-modulating polypeptide;

b) a gene encoding a complement control polypeptide, wherein the mutation results in the virus lacking at least one functional complement control polypeptide;

c) a gene encoding a TNF-modulating polypeptide, wherein the mutation results in the virus lacking at least one functional TNF-modulating polypeptide;

d) a gene encoding a serine protease inhibitor, wherein the mutation results in the virus lacking at least one functional serine protease inhibitor;

e) a gene encoding an IL-1β modulator polypeptide, wherein the mutation results in the virus lacking at least one functional IL-1β modulator polypeptide;

f) a gene encoding a functional A41L, B7R, N1L or vCKBP chemokine binding polypeptide or C11R EGF-like polypeptide, wherein the mutation results in the virus lacking at least one function of A41L, B7R, N1L, vCKBP, or C11R; or

g) a gene encoding a polypeptide, wherein the mutation results in an increase in infectious EEV form of vaccinia virus.

7. The attenuated vaccinia virus of claim 1, wherein the virus is the Copenhagen or Western Reserve strain comprising the mutation in the first gene encoding an interferon-modulating polypeptide.

8. The attenuated vaccinia virus of claim 1, wherein the interferon-binding polypeptide is B8R or B18R.

9. The attenuated vaccinia virus of claim 6, comprising the mutation in a gene encoding a second interferon-modulating polypeptide that results in the virus lacking at least a second functional second interferon-modulating polypeptide.

10. The attenuated vaccinia virus of claim 9, wherein the functional second interferon-modulating polypeptide is B8R, B18R, B13R, E3L, or vC12L.

11. The attenuated vaccinia virus of claim 10, wherein the virus lacks functional B8R.

12. The attenuated vaccinia virus of claim 10, wherein the virus lacks functional B13R.

13. The attenuated vaccinia virus of claim 10, wherein the virus lacks functional B8R and B13R.

14. The attenuated vaccinia virus of claim 13, wherein the virus lacks functional B8R, B13R, and vC12L.

15. The attenuated vaccinia virus of claim 14, wherein the virus further lacks functional B28R or A53R.

16. The attenuated vaccinia virus of claim 15, wherein the virus lacks functional B28R and A53R.

17. The attenuated vaccinia virus of claim 14, wherein the virus further lacks functional B18R.

18. The attenuated vaccinia virus of claim 17, wherein the virus further lacks functional B28R or A53R.

19. The attenuated vaccinia virus of claim 18, wherein the virus lacks functional B28R and A53R.

20. The attenuated vaccinia virus of claim 1, comprising the mutation in a gene encoding a complement control polypeptide that results in the virus lacking at least one functional complement control polypeptide.

21. The attenuated vaccinia virus of claim 20, wherein the functional complement control polypeptide is VCP.

22. The attenuated vaccinia virus of claim 6, comprising the mutation in a gene encoding a TNF-modulating polypeptide that results in the virus lacking at least one functional TNF-modulating polypeptide.

23. The attenuated vaccinia virus of claim 22, wherein the functional TNF-modulating polypeptide is A53R, B28R, or vCKBP.

24. The attenuated vaccinia virus of claim 6, comprising the mutation in a gene encoding a serine protease inhibitor that results in the virus lacking at least one functional serine protease inhibitor.

25. The attenuated vaccinia virus of claim 24, wherein the serine protease inhibitor is B13R, B22R, or K2L.

26. The attenuated vaccinia virus of claim 6, comprising the mutation in a gene encoding an IL-1β modulator that results in the virus lacking at least one functional IL-1β modulator.

27. The attenuated vaccinia virus of claim 26, wherein the functional IL-1β modulating polypeptide is B13R or B15R.

28. The attenuated vaccinia virus of claim 6 comprising a mutation in a gene encoding a functional A41L, B7R, N1L or vCKBP chemokine binding polypeptide or C11R EGF-like polypeptide.

29. The attenuated vaccinia virus of claim 28, wherein the polypeptide is B7R, vCKBP, or N1L.

30. The attenuated vaccinia virus of claim 28, wherein the polypeptide is A41L, vCKBP, or C11R.

31. The attenuated vaccinia virus of claim 6, comprising the mutation that results in an increase in production of infectious EEV form of vaccinia virus.

32. The attenuated vaccinia virus of claim 31, wherein the mutation causing an increase in infectious EEV form is in the gene encoding A34R or B5R.

33. The attenuated vaccinia virus of claim 32, wherein the mutation causing an increase in infectious EEV form is in the gene encoding A34R.

34. The attenuated vaccinia virus of claim 33, wherein the mutation in A34R is a K151D mutation.

35. The attenuated vaccinia virus of claim 6, wherein the virus comprises more at least two different mutations in a), b), c), d), e), f) or g).

36. The attenuated vaccinia virus of claim 35, wherein the virus comprises a mutation in g) and at least a mutation in a), b), c), d), e) or f).

37. The attenuated vaccinia virus of claim 1, wherein the virus is comprised in a pharmaceutical composition.

38. The attenuated vaccinia virus of claim 37, wherein the composition further comprises interferon.

39. The attenuated vaccinia virus claim of claim 37, wherein the composition further comprises an anti-cancer agent.

40. The attenuated vaccinia virus of claim 39, wherein the anti-cancer agent is an antibody, a chemotherapeutic, or a nucleic acid encoding a tumor suppressor.

41. An attenuated vaccinia virus comprising a first mutation that results in the virus lacking a functional vC12L polypeptide.

42. The attenuated vaccinia virus of claim 41, further comprising a second mutation in at least one of the following:

a) a gene encoding an interferon-modulating polypeptide that results in the virus lacking at least a second functional interferon-modulating polypeptide;
b) a gene encoding a complement control polypeptide, wherein the mutation results in the virus lacking at least one functional complement control polypeptide;
c) a gene encoding a TNF-modulating polypeptide, wherein the mutation results in the virus lacking at least one functional TNF-modulating polypeptide;
d) a gene encoding a serine protease inhibitor, wherein the mutation results in the virus lacking at least one functional serine protease inhibitor;
e) a gene encoding an IL-1β modulator polypeptide, wherein the mutation results in the virus lacking at least one functional IL-1β modulator polypeptide;
f) a gene encoding a functional A41L, B7R, N1L or vCKBP chemokine binding polypeptide or C11R EGF-like polypeptide, wherein the mutation results in the virus lacking at least one function of A41L, B7R, N1L, vCKBP, or C11R; or
g) a gene encoding a polypeptide, wherein the mutation results in an increase in infectious EEV form of vaccinia virus.

43. The attenuated vaccinia virus of claim 41, wherein the virus is the Copenhagen or Western Reserve strain comprising the mutation in the first gene encoding an interferon-modulating polypeptide.

44. The attenuated vaccinia virus of claim 41, comprising a second mutation in gene encoding an interferon-modulating polypeptide that results in the virus lacking at least a second functional interferon-modulating polypeptide.

45. The attenuated vaccinia virus of claim 44, wherein the second functional interferon-modulating polypeptide is B8R, B13R, or B18R.

46. An attenuated vaccinia virus comprising a first mutation that results in the virus lacking a functional B15R polypeptide.

47. The attenuated vaccinia virus of claim 46, further comprising a second mutation in at least one of the following:

a) a gene encoding an interferon-modulating polypeptide that results in the virus lacking at least a functional interferon-modulating polypeptide;
b) a gene encoding a complement control polypeptide, wherein the mutation results in the virus lacking at least one functional complement control polypeptide;
c) a gene encoding a TNF-modulating polypeptide, wherein the mutation results in the virus lacking at least one functional TNF-modulating polypeptide;
d) a gene encoding a serine protease inhibitor, wherein the mutation results in the virus lacking at least one functional serine protease inhibitor;
e) a gene encoding an IL-1β modulator polypeptide, wherein the mutation results in the virus lacking at least one functional IL-1β modulator polypeptide;
f) a gene encoding a functional A41L, B7R, N1L or vCKBP chemokine binding polypeptide or C11R EGF-like polypeptide, wherein the mutation results in the virus lacking at least one function of A41L, B7R, N1L, vCKBP, or C11R; or
g) a gene encoding a polypeptide, wherein the mutation results in an increase in infectious EEV form of vaccinia virus.

48. The attenuated vaccinia virus of claim 47, wherein the virus comprises a mutation in a gene encoding an interferon-modulating polypeptide or encoding a TNF-modulator.

49. The attenuated vaccinia virus of claim 48, wherein the interferon modulating polypeptide is B13R and the TNF-modulator is B29R.

50. A method for treating a cancer cell comprising administering to the cancer cell an effective amount of a vaccinia virus unable to express at least one of the following:

a) a functional first interferon-modulating polypeptide;
b) a functional complement control polypeptide;
c) a functional TNF-modulating polypeptide;
d) a functional serine protease inhibitor;
e) a functional IL-1β modulating polypeptide;
f) a functional non-infectious EEV form polypeptide;
g) a functional A41L, B7R, N1L, vCKBP, or C11R polypeptide.

51. The method of claim 50, wherein the attenuated vaccinia virus lacks more than one of the following:

a) a functional first interferon-modulating polypeptide;
b) a functional complement control polypeptide;
c) a functional TNF-modulating polypeptide;
d) a functional serine protease inhibitor;
e) a functional IL-1β modulating polypeptide;
f) a functional anti-infectious EEV form polypeptide;
g) a functional A41L, B7R, N1L, vCKBP, or C11R polypeptide; or
h) a functional second interferon-modulating polypeptide.

52. The method of claim 50, wherein the vaccinia virus lacks a functional first interferon-modulating polypeptide.

53. The method of claim 52, wherein the vaccinia virus is Copenhagen or Western Reserve strain.

54. The method of claim 51, wherein the functional first or second interferon-modulating polypeptide lacking in the virus is B18R or B8R.

55. The method of claim 50, wherein the virus lacks at least one functional complement control polypeptide.

56. The method of claim 55, wherein the functional complement control polypeptide lacking in the virus is VCP.

57. The method of claim 50, wherein the virus lacks at least one functional TNF-modulating polypeptide.

58. The method of claim 57, wherein the functional TNF-modulating polypeptide lacking in the virus is A53R, B28R, or vCKBP.

59. The method of claim 50, wherein the virus lacks at least one functional serine protease inhibitor.

60. The method of claim 59, wherein the serine protease inhibitor is B13R, B22R, or K2L.

61. The method of claim 50, wherein the virus lacks at least one functional IL-1β modulator.

62. The method of claim 61, wherein the IL-1β modulator is B13R or B15R.

63. The method of claim 50, wherein the virus lacks at least one functional anti-infectious EEV form polypeptide.

64. The method of claim 63, wherein the attenuated vaccinia virus comprises a K151D mutation in the anti-infectious EEV form polypeptide A34R or mutation in the gene encoding B5R.

65. The method of claim 50, further comprising administering interferon to the cell.

66. The method of claim 65, wherein the interferon is IFNα, IFNβ, or IFNγ.

67. The method of claim 50, wherein the attenuated vaccinia virus is compromised in a pharmaceutically acceptable composition.

68. The method of claim 50, wherein the cancer cell is a tumor cell.

69. The method of claim 50, wherein the cancer cell is in a patient.

70. The method of claim 69, wherein the attenuated vaccinia virus is administered to the patient directly, endoscopically, intratracheally, intratumorally, intravenously, intralesionally, intramuscularly, intraperitoneally, regionally, percutaneously, or subcutaneously.

71. The method of claim 69, wherein the patient has a solid tumor.

72. The method of claim 71, further comprising resecting all or part of the solid tumor.

73. The method of claim 72, wherein the attenuated vaccinia virus is administered to the patient prior to tumor resection.

74. The method of claim 73, wherein the attenuated vaccinia virus is administered to the patient after tumor resection.

75. The method of claim 69, further comprising administering to the patient chemotherapy or radiotherapy.

76. The method of claim 75, wherein chemotherapy is administered to the patient at least once.

77. The method of claim 76, wherein the chemotherapy is cisplatin (CDDP), carboplatin, procarbazine, mechlorethamine, cyclophosphamide, camptothecin, ifosfamide, melphalan, chlorambucil, bisulfan, nitrosurea, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicomycin, mitomycin, etoposide (VP16), tamoxifen, taxotere, taxol, transplatinum, 5-

fluorouracil, vincristin, vinblastin, methotrexate, gemcitabine, oxaliplatin, irinotecan, topotecan, or any analog or derivative variant thereof.

78. The method of claim 75, wherein radiotherapy is administered at least once to the patient.

79. The method of claim 78, wherein X-ray irradiation, UV-irradiation, γ-irradiation, electron-beam radiation, or microwaves are administered at least once to the patient.

80. The method of claim 50, wherein the cancer cell is a bladder, blood, bone, bone marrow, brain, breast, colorectal, esophagus, gastrointestine, head, kidney, liver, lung, nasopharynx, neck, ovary, pancreas, prostate, skin, stomach, testicular, tongue, or uterus cell.

81. The method of claim 50, wherein the attenuated vaccinia virus is administered more than one time.

82. The method of claim 50, wherein the attenuated vaccinia virus further comprises a nucleic acid sequence encoding a heterologous therapeutic polypeptide.

83. The method of claim 82, wherein the heterologous therapeutic polypeptide is a tumor suppressor, immunomodulator, angiogenesis inhibitor, anti-vascular polypeptide, cytotoxic polypepitde, apoptosis inducer, pro-drug activating enzyme, or cytostatic polypeptide.

84. The method of claim 50, further comprising administering to the cell a protease or peptidase.

85. The method of claim 50, wherein the attenuated vaccinia virus is IHD-J strain or comprises a K151D mutation in A34R or comprises a mutation in the gene encoding B5R.

86. The method of claim 50, wherein the attenuated vaccinia virus is produced from a cell line that overexpresses at least one human complement inhibitory protein.

87. The method of claim 86, wherein the complement inhibitory protein is CD55, CD46, or CD59.

88. The method of claim 50, further comprising administering to the cell a microtubule stabilizing agent.

89. The method of claim 88, wherein the microtubule stabilizing agent is taxane.

90. A method for treating cancer in a patient comprising administering to the patient an effective amount of a pharmaceutically acceptable composition comprising an attenuated vaccinia virus comprising a mutation in the gene encoding B8R, B18R, or vC12L.

91. The method of claim 90, wherein the pharmaceutically acceptable composition further comprises interferon or a nucleic acid encoding interferon.

92. The method of claim 90, wherein the attenuated vaccinia virus lacks a functional B8R, B18R, or vC12L polypeptide.

93. The method of claim 92, wherein the attenuated vaccinia virus lacks a functional B8R or vC12L polypeptide and further comprises a mutation in a gene encoding B13R, wherein the virus lacks a functional B13R polypeptide.

94. The method of claim 93, wherein the attenuated vaccinia virus lacks functional B8R, vC12L, and B13R polypeptides.

95. The method of claim 92, wherein the attenuated vaccinia virus lacks at least two functional B8R, B18R, or vC12L polypeptides.

96. The method of claim 95, wherein the attenuated vaccinia virus lacks a functional B8R, B18R, and vC12L polypeptide.

97. The method of claim 92, wherein the attenuated vaccine virus is further unable to express at least one of the following:

a) a functional complement control polypeptide;

b) a functional TNF-modulating polypeptide

c) a functional serine protease;

d) a functional IL-1β modulator;

e) a functional A41L, B7R, N1L, vCKBP, or C11R polypeptide; or

f) a functional anti-infectious EEV form polypeptide.

98. The method of claim 94, wherein the attenuated vaccine virus is further unable to express at least one of the following:

a) a functional complement control polypeptide;

b) a functional TNF-modulating polypeptide

c) a functional serine protease;

d) a functional IL-1β modulator;

e) a functional A41L, B7R, N1L, vCKBP, or C11R polypeptide; or

f) a functional anti-infectious EEV form polypeptide.

99. A method for killing a cancer cell comprising contacting the cancer cell with an attenuated vaccinia virus having a reduced ability to inhibit an antiviral response mediated by an interferon, a chemokine, a cytokine, complement, or neutralizing antibody.

100. The method of claim 99, wherein the attenuated vaccinia virus has a mutation in a nucleic acid sequence encoding B8R, B13R, B18R, or vC12L.

101. The method of claim 99, wherein the attenuated vaccinia virus is unable to express at least one of the following:

a) a functional interferon-modulating polypeptide

b) a functional complement control polypeptide;

c) a functional TNF-modulating polypeptide

d) a functional serine protease;

e) a functional IL-1β modulator;

f) a functional A41L, B7R, N1L, vCKBP, or C11R polypeptide;or

g) a functional anti-infectious EEV form polypeptide.

102. A method of treating cancer in a cancer patient, comprising contacting a tumor site with a therapeutically effective amount of an attenuated vaccinia virus and an agent that increases

antitumoral efficacy of the attenuated vaccinia virus, wherein expression of the vaccinia virus and agent that increases antitumoral efficacy results in treatment of the cancer.

103. The method of claim 102, wherein the agent that increases the antitumoral efficacy of the attenuated vaccinia virus is an interferon, proteinase, peptidase, microtubule stabilizing agent, chemotherapy, radiotherapy, gene therapy, immunotherapy, and immunomodulatory therapy.

104. A method for producing a fortified EEV form of vaccinia virus comprising:

a) infecting a human cell line that overexpresses a complement inhibitory protein with a vaccinia virus;

b) isolating the EEV form of the vaccinia virus from the infected cell.

105. The method of claim 104, wherein the vaccinia virus comprises a mutation in the gene encoding A34R protein, wherein the mutation results in a K151D mutation.

106. The method of claim 104, wherein the complement inhibitory protein is CD55, CD46, or CD59.

107. The method of claim 104, wherein the human cell line overexpresses more than one complement inhibitory protein.

108. A method for treating microscopic residual cancer comprising:

(i) identifying a patient having a resectable tumor;

(ii) resecting the tumor; and

(iii) contacting the tumor bed with a vaccinia virus having at least one mutation in a gene encoding A34R, A41L, A53R, B5R, B7R, B8R, B13R, B15R, B18R, B22R, B28R, B29R, C11R, E3L, K2L, N1L, vC12L, or vCKBP.

109. A method for treating a subject having a tumor comprising:

(i) surgically revealing the tumor; and

(ii) contacting said tumor with an attenuated vaccinia virus lacking A34R, A41L, A53R, B5R, B7R, B8R, B13R, B15R, B18R, B22R, B28R, B29R, C11R, E3L, K2L, N1L, vC12L, or vCKBP function.

110. A method for treating a subject having a tumor comprising perfusing the tumor, over an extended period of time, with an attenuated vaccinia virus.

111. A method of inhibiting metastatic disease in a subject having cancer comprising administering to the subject an attenuated vaccinia virus, thereby conferring a therapeutic benefit on the subject.

112. A method of treating a multidrug-resistant tumor in a patient comprising i) administering to the patient an attenuated vaccinia virus and ii) administering chemotherapy or radiotherapy to the patient, thereby conferring a therapeutic benefit on the subject.

113. A method of rendering an unresectable tumor in a patient resectable comprising administering to the patient an effective amount of an attenuated vaccinia virus and resecting all or part of the tumor.

114. A method of treating a cancer patient whose cancer is resistant to chemotherapy or radiotherapy comprising administering to the patient an attenuated vaccinia virus and administering chemotherapy or radiotherapy to the patient.

115. A composition comprising vaccinia virus in which the composition is at least 50% fortified EEV form of vaccinia virus.

116. The composition of claim 115, wherein the composition is at least 60% fortified EEV form of vaccinia virus.

117. The composition of claim 116, wherein the composition is at least 70% fortified EEV form of vaccinia virus.

118. A human cell line for the production of fortified EEV form of vaccinia virus, comprising vaccinia virus and overexpressing at least one complement inhibitory polypeptide.

119. The human cell line of claim 118, wherein the complement inhibitory polypeptide is CD55, CD46, or CD59.

120. The human cell line of claim 118, wherein the vaccinia virus is unable to express at least one of the following:

a) a functional interferon-modulating polypeptide

b) a functional complement control polypeptide;

c) a functional TNF-modulating polypeptide

d) a functional serine protease;

e) a functional IL-1β modulator;

f) a functional anti-infectious EEV form polypeptide; or

g) a functional A41L, B7R, N1L, or vCKBP chemokine binding polypeptide or a C11R EGF-like polypeptide.